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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

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Accidental Radioactive Contamination of Human and Animal Feeds and Potassium Iodide as a Thyroid-Blocking Agent in a Radiation Emergency

Recommendations For State and Local Agencies and Request for Submissions of New Drug Applications

[4110-03-M]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 1090]

[Docket No. 76N-0050]

ACCIDENTAL RADIOACTIVE CONTAMINATION OF HUMAN FOOD AND ANIMAL FEEDS

Recommendations for State and Local Agencies

AGENCY: Food and Drug Administration.

ACTION: Proposed Recommendations.

SUMMARY: This document provides guidelines and recommendations for action to be taken in the event of a radiological incident resulting in the contamination of human food or animal feeds. These guidelines and recommendations are for use by State and local agencies responsible for constructing response plans in the event of a radiological incident. The proposal would establish a set of guidelines that can be used to determine whether or not levels of radiation encountered in food after a radiological incident warrant protective action and would suggest appropriate actions that may be taken if action is warranted. This proposal is being made because the Food and Drug Administration (FDA) has a responsibility to issue guidance on appropriate planning actions neccessary for evaluating and preventing contamination of foods and animal feeds and on the control and use of such products, should they become contaminated.

DATE: Comments by February 13, 1979.

ADDRESSES: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857; copy of supporting data to the Bureau of Radiological Health (HFX-440), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

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SUPPLEMENTARY INFORMATION: The purpose of these proposed recommendations is to provide guidance to State and local agencies for use in the development of emergency plans and for use in the emergency response to incidents involving the contamination of food and animal feeds by radioactive materials. The guidance contains basic criteria, defined as protective action guides (PAG's), for establishing the level of radioactive contamination at which action should be taken to protect the public health and assure the safety of food. This document also proposes specific guidance on what emergency protective actions should be taken to prevent further contamination or restrict the use of food, as well as more general guidance on the development and implementation of emergency action. The protective action guides (PAG's) have been developed on the basis of a risk evaluation to identify that level of contamination where action is necessary to assure the safe use of food.

BACKGROUND

This proposed guidance on accidental radioactive contamination of food from fixed nuclear facilities, transportation accidents, and fallout is part of a Federal interagency effort coordinated by the Federal Preparedness Agency, General Services Administration. The Nuclear Regulatory Commission is the lead agency and among other activities has published a "Guide and Checklist for Development and Evaluation of State and Local Government Radiological Emergency Response Plans in Support of Fixed Nuclear Facilities" (NUREG-75/111 Dec. 1974).

The Federal Preparedness Agency issued a notice in the FEDERAL REGISTER of December 24, 1975 (40 FR 59494) which reflected governmental reorganizations and reassigned agency responsibilities for radiological incident emergency response planning.

Among the responsibilities of the Department of Health, Education, and Welfare (HEW) is "Issuance of guidance on appropriate planning actions necessary for evaluating and preventing radioactive contamination of foods and animal feeds and the control and use of such products should they become contaminated." Within HEW this function has been delegated to the Commissioner of Food and Drugs.

In the preparation of this proposal, FDA has reviewed the protective action guidance adopted by the Federal Radiation Council (FRC) (Refs. 8 and 9). The Federal Radiation Council was created to provide guidance to the Federal agencies on radiation protection standards.

Although the Federal Radiation Council no longer exists and its functions have been transferred to the Environmental Protection Agency (EPA), FRC expected that each Federal agency, by virtue of its immediate knowledge of its operating problems, would use the applicable FRC guides (Refs. 6 through 9) as a basis for developing detailed standards to meet the particular needs of the agency. Historically, recommendations on radiation protection have involved a judgmental analysis that balances the health hazards associated with radiation against the benefits of using radiation. These benefits include the use of radiation in industry, research, and diagnosis and treatment of disease, and in providing new sources of energy.

Scientific findings indicate that human exposure to radiation can induce genetic and somatic effects. Although current evidence is insufficient to prove with certainty the nature of the dose-effect relationship at low doses and dose rates (which are doses per unit of time) present radiation protection practice assumes a direct linear relationship between the probability of biological effect occurring and the amount of dose. By extrapolation from high-dose and dose-rate experimental and epidemiological data to low doses and dose rates, it becomes possible to estimate the probability of biological effects from low doses. It is generally agreed that the frequency with which an effect may actually occur will not exceed the frequency predicted by this assumption. In any case, a basic principle of radiation protection is to keep exposure to radiation as low reasonably achievable.

The FRC guides (Refs. 6 through 9) have served as the basic guidance for control of environmental radiation. Since the publication of these documents, data on radiation risks have been reviewed in light of additional information on biological effects that became available (Ref. 10), and environmental standards for nuclear power operations have been specifically defined by EPA (see the FEDERAL REGISTER of January 13, 1977 (42 FR 2858)). Thus, it is appropriate for FDA to issue response-planning recommendations which consider recent radiation risk and measurement data for use in the event of a contaminating radiation incident.

THE PROPOSED RECOMMENDATIONS

Proposed § 1090.400(b) defines a PAG as the projected radiation dose equivalent or dose commitment to individuals in the general population that warrants protective action following a release of radioactive material. Protective action would be warranted if the expected individual dose reduction is not offset by negative social, economic, or health effects. A negative impact could, for example, occur if an adequate alternative food supply is not available. The PAG does not include the radiation dose that has occurred before the assessment, nor do these recommendations imply an acceptable radiation dose from food containing radioactivity during normal

conditions. Rather, their purpose is to prevent additional radioactivity from entering the human food chain and to reduce or avoid future radiation doses to the population after an accidental contaminating event. Such events include accidents at nuclear facilities, transportation accidents, and fallout from nuclear devices. The proposed protective actions are intended for implementation within hours or days from the time an emergency is recognized, and their duration should not be expected to exceed 1 or 2 months, based on previous experience with atmospheric fallout. Long-term regulation of radioactivity in the environment is the responsibility of the Environmental Protection Agency.

These recommendations would define projected radiation dose equivalent limits, exclusive of doses contributed by natural radioactivity, at which appropriate actions are suggested. The basic unit used in these recommendations is the radiation dose equivalent, defined in proposed § 1090.400(b) as "a quantity that expresses all radiation on a common scale for calculating the effective absorbed dose. It is defined as the product of the absorbed dose in rads and certain modifying factors. The unit of dose equivalent is the rem." "Dose commitment" means the radiation dose equivalent, delivered over a lifetime, from a single event received by an exposed individual to the organ cited. Ideally, if a particular tissue is subject to radiation from more than one source, the combined dose from all sources should be considered. However, in an accident at a fixed nuclear facility the food chain is likely to be the major route of significant population exposure (Ref. 1). For the purpose of these recommendations, the Commissioner has considered only the food pathway because FDA authority specifically relates to food and animal feeds. The proposed recommendations assume that the population group receiving radiation doses via the food chain receives only insignificant doses from other pathways, e.g., external radiation or inhalation.

PAG's are proposed in § 1090.400(c) for two levels of response:

1. Preventive PAG—applicable to situations where protective actions causing minimal impact on the food supply are appropriate. A Preventive PAG establishes a level at which responsible officials should take protective action to prevent or reduce the concentration of radioactivity in food or animal feed.

2. Emergency PAG—applicable to incidents where protective actions of great impact on the food supply are justified because of the projected health hazards. An Emergency PAG establishes a level at which responsible officials sould isolate food containing radioacitivity to prevent its introduction into commerce, and at which the responsible officials must determine whether condemnation or another disposition is appropriate.

Proposed § 1090.400(d) lists derived response levels in the following terms: initial ground deposition (activity per unit of area), the concentration of radioactivity in milk (activity per unit of volume) or pasture (activity per unit of weight), and total dietary intake (total activity) that corresponds to these two PAG's. Thus, the derived response levels provide concentrations of specific radionuclides in specific media that can be directly compared to the levels of measured radioactivity to assure rapid and effective protective actions.

The recommendations in § 1090.400(e) provide guidance on the implementation of the PAG's for other food items, animal feeds, radionuclide mixtures, and other critical organs. The sampling sites are identified in § 1090.400(f), and references to recommended methods of analysis are provided in § 1090.400(g).

These recommendations proposed in § 1090.400(h) appropriate actions at Preventive and Emergency PAG response levels that are recommended within the context of the health benefit that may be achieved through the prevention of unnecessary radiation exposure.

PUBLIC COMMENTS

In the FEDERAL REGISTER of May 7, 1976 (41 FR 18897) the Commissioner invited interested persons to submit data, information, and views on guidelines for planning emergency response to radiological incidents that may result in radioactive contamination of human food and animal feeds. The Commissioner received and considered the following suggestions and views in preparing the proposed recommendations:

a. In radiation incidents involving a potential threat to the public health, recommendations in terms of specific radionuclide quantities, such as activity per unit volume or weight, are most easily applied.

b. Guidance should be based on evaluation of potential health risks associated with radiation levels at which protective action would be recommended and on cost-benefit analysis of various options available for preventing and reducing radiation exposure via the food pathway.

c. Proposed recommendations should be based on the potential radiation hazard to designated critical organs. They should consider the specific exposure and metabolic pathways, the radiobiological characteristics of individual radionuclides, and the radiosensitivity of the most critical group in the exposed population.

d. Proposed recommendations should be generally adaptable over a wide range of conditions, have a rapid response time, and be limited to the immediate emergency situation.

Based on responses to the May 1976 notice and other available data, proposed recommendations were drafted and distributed on December 7, 1976 to interested individuals, all States having radiological health programs, Federal agencies involved in radiological health programs, and Federal agencies involved in radiological emergency response planning. Some 24 respondents offered more than 100 pages of comments. A summary of the most pertinent comments and the Commissioner's response to them follows:

1. Many comments pointed out that responsibilities for formulating guidelines on radioactivity in foods seem to overlap, thus leading to an apparent duplication of effort. In general, these comments stated or assumed that the Environmental Protection Agency (EPA) was to set the PAG's; in fact, EPA has already done so for external radiation, i.e., radiation from fixed sources, and inhalation, i.e., airborne radiation, (Ref. 5). The comments nonetheless did recognize that setting guidance for foods falls within the purview of FDA. The consensus among the comments was that there should be cooperation between EPA and FDA, and that all Federal recommendations about radioactivity in foods and animal feeds should be compatible.

The Commissioner recognizes that several of the Federal responsibilities overlap. However, the Interagency Agreement (see the FEDERAL REGISTER of December 24, 1975 (40 FR 59494)), made EPA responsible for "Establishment of protection action guides in coordination with appropriate Federal agencies," and HEW responsible for "Issuance of guidance on appropriate actions necessary for evaluating and preventing radioactive contamination of foods and animal feeds and the control and use of such products should they become contaminated." The Director, Bureau of Radiological Health, FDA, and the Deputy Assistant Administrator for Radiation Programs, EPA, established an official liaison to assure an exchange of opinion and information and to avoid a duplication of effort on the proposed FDA recommendations on radioactivity in foods.

2. Several comments requested a clarification of the relevance of prohibitions in section 409 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 348) to radioactive contamination of foods.

In the FEDERAL REGISTER of September 30, 1977 (42 FR 52814), FDA estab-

lished procedures for regulating food contaminants and naturally occurring poisonous or deleterious substances in food. In § 109.6 (21 CFR 109.6) the Commissioner recognizes that when a food contaminant is unavoidable but cannot be approved under the criteria of section 409 of the act, a procedure to control its use under authority of sections 306, 402(a), and 406 of the act (21 U.S.C 336, 342(a), 346) is still available. Accidental radioactive contamination of food for man or animals may fall within the scope of these provisions. Moreover, the Commissioner advises that establishing guidelines for radionuclide contamination of foods is required to meet HEW's responsibility as specified in the December 1975 notice. For these reasons the Commissioner concludes that such action is in complete accord with the act.

3. Several comments asked whether milk containing radioactivity at a specific level could be diluted with milk at a lower radioactive concentration so the resultant product could be consumed.

There is a longstanding FDA policy against blending, which is the intentional adulteration of unadulterated food with contaminated or adulterated food (see generally 21 CFR Parts 109 and 509). It is the agency's position that blending adulterates the unadulterated food in violation of section 402(a)(1) of the act. The agency does, however, permit the diversion of contaminated human food into use as animal feed when such diversion would pose no significant risk to human or animal health. The Commissioner believes diversion of milk contaminated from a radiological incident should be considered on a case-by-case basis to evaluate the potential for ultimate contamination of human food and the risk to man and animals.

4. Some reviewers questioned the use of the linear nonthreshold hypothesis as a basis for risk analysis because they believe that it underestimates risk. A related comment suggested that both fatal and nonfatal health risks, and genetic as well as somatic effects, be examined to define each proposed PAG level.

The Commissioner believes the linear nonthreshold approach to somatic risk evaluation is the most prudent approach. Hence, the Commissioner is proposing that it be employed in these evaluation. Genetic risks were also considered, but the adequacy of existing data does not allow as precise an estimate of those risks. Also, nonfatal effects were not deemed valid as an endpoint for risk analysis because "health effects" and "ill health" are biological endpoints that are difficult, if not impossible, to quantify. In sum, the Commissioner concludes that the linear model is sufficiently conservative that it provides an adequate margin of safety for these nonquantifiable effects and has adopted it for assessing the risks of all health effects.

5. Several comments argued that the rationale for the PAG values (especially the Preventive and Emergency PAG's) were based on old information that could be replaced with newer data. These comments also suggested defining the PAG's in terms of the dose commitment to the critically exposed population i.e., children less than 1 year of age), rather than a "suitable sample" (which in turn is defined as children less than 1 year of age). They proposed these definitions to avoid any confusion that "suitable sample" might refer to food or animal feed rather than to human beings as intended in the draft (i.e., a "suitable sample" of the exposed population). Furthermore, use of a critically exposed population would eliminate the one-third factor used as an operational technique and associated with a projected dose to a "suitable sample" of the exposed population.

One comment stated that although the use of a "suitable sample" has historical precedence, its use was not adequately justified in the draft. Another reviewer suggested just the reverse; namely, that information applicable only to the operational technique concept and not the critically exposed population concept be cited in any recommendations. In any case, there is a consensus that a single defined exposed group should be selected as a basis for making the necessary calculations.

For the sake of simplicity and to be consistent with other Federal agency guidelines, the concept of a "suitable sample" is no longer employed. Rather, the Commissioner proposes to define PAG levels in terms of projected dose to an exposed individual in the critical segment of the population (i.e., persons receiving the greatest dose per unit intake and having the greatest sensitivity).

6. One reviewer recommended that the fetus be considered the critically exposed population for iodine-131.

The Commissioner advises that the problem has been evaluated by several investigators (Refs. 3 and 4), who found that the newborn infant and not the fetus has the highest iodine-131 uptake per gram of thyroid tissue. The Commissioner believes this group should constitute the critical segment of the population.

7. Several comments suggested removal or modification of the Alert PAG, which was included in the original draft, because:

a. Appropriate protective actions are not recommended.

b. The informational and administrative actions that are suggested are covered by other standards and regulations.

c. At times the major protective action at this level (e.g., control at source) is not possible within the framework of situations the recommendations are designed to cover, nor, as one reviewer points out, is this action within the scope of FDA responsibilities.

d. Sampling and analysis at the Alert PAG response levels would be difficult and expensive, especially on a nationwide basis.

e. The Alert PAG lends itself to misinterpretation by the public; if used, it should emphasize more strongly the extremely low levels of contamination it represents.

f. As presently conceived, the PAG's apply to an acute abnormal situation; the Alert PAG, evaluated in terms of chronic contamination (perhaps from normal operations) and long-term effects, is confusing when applied to abnormal situations. Further complications exist because the Alert PAG presents radionuclide concentrations in terms of average yearly concentration, while the other PAG's present the response level concentrations in terms of peak concentrations.

Based on these extensive comments, the Commissioner has deleted the Alert PAG concept.

8. Several comments noted that the problem of multiple contaminating events was not addressed in the December 1976 draft.

The Commissioner agrees that the draft recommendation did not directly address the possibility that the projected dose associated with a specific PAG could be exceeded by multiple events, each one of which by itself would not exceed the PAG. However, the proposed recommendation would express radioactivity in food in terms of total intake (microcuries) at which the projected dose would be equal to or exceed the PAG. The Commissioner believes this provides an option for the emergency planner to utilize in the event of multiple contaminating events.

9. One comment submitted evidence that the shelf life of milk can be extended by storage at lowered temperature, provided ultrahigh heat treatment is employed in processing.

The Commissioner has incorporated this procedure as a feasible protective action that will allow the decay of iodine-131 in contaminated milk.

10. One comment noted that the recommendations imply an ongoing routine sampling program capable of detecting levels of radioactivity associated with the PAG's. The comment asked whether such a system exists or whether FDA would assume responsi-

bility for future operation of such a system.

The Commissioner advises that there is no extensive routine national program of sampling and analysis of radioactivity in food. As noted in paragraph 7 of this preamble, the Alert PAG has been deleted, and the recommendations no longer imply the need for an ongoing routine sampling program. In the event of an incident, the sampling programs required would be provided by State and local agencies and the nuclear facilities with the assistance of Federal agencies. This has been the agency's experience.

11. Another comment asked whether actions taken when the projected dose is exceeded are based on calculation from air concentrations from accidentally released radioactivity or from food that is actually contaminated.

The Commissioner notes that under the Federal Food, Drug and Cosmetic Act, action can be taken only on evidence that the food may be rendered injurious to health. In a protective action involving avoidance of projected doses, action may be appropriate based upon air concentration or ground deposition. However, action based solely on radioactive air concentrations is beyond the scope of these recommendations.

Rationale for the PAG's

The process of determining numerical limits for setting radiation standards has traditionally been one of risk assessment. The process of risk assessment consists of two elements: Determination of the probability that an event will occur, and determination of "acceptable risk." Because initiation of protective action assumes that an incident has occurred, the emphasis in this case will be on the determination of acceptable risk or safety. A recent discussion of acceptable risk defines risk as a measure of the probability and severity of adverse effects and defines safety as the degree to which risks are judged acceptable (Ref. 13). The Commissioner agrees that safety involves a judgment as to the acceptability of the risks but recognizes that there may not be universal agreement because various individuals may not all judge a given risk to be acceptable. Thus, the PAG's proposed here represent the Commissioner's judgment as to that level of contamination resulting from radiation incidents at which protective actions should be taken to protect the public health.

To provide a basis for this judgment, the risk of radiation exposure was compared to the risk of prevalent hazards accepted by society and to the variability of the natural radiation environment. The numerical dose commitment values that were derived are comparable to the risk from natural disasters (approximately a one in a million annual individual risk of death) and to the risk associated with two standard errors of the mean (the 95% confidence level) of the natural radiation environment in the United States (8.5 millirem per year). Both somatic risks (cancer deaths) based on an absolute risk model (Ref. 10) and genetic effects have been assessed in this evaluation. An absolute risk approach (estimates of deaths per rem of dose) was used in preference to a relative risk model because a relative risk model is based on natural cancer rates. Natural cancer rates are highly variable and depend upon such diverse factors as age, location, socioeconomic class, race, genetic makeup, and environmental factors.

For the Preventive PAG the most conservative estimates assume a dose commitment to the whole U.S. population that is associated with the somatic risk equivalent to two standard errors of the mean of the natural radiation environment. This statistic is a measure of the variability or scatter of the average doses of natural radioactivity amongst the states. These dose commitments are approximately 0.47 rem to the whole body, bone marrow, or other organs, and 1.4 rem to the thyroid.

In the case of the Emergency PAG, it is reasonable to expect a smaller population would be affected; and the value 15 million has been assumed, this being the estimated maximum population within 25 miles of present reactor sites. These population assumptions yield values for the Emergency PAG of 7 rem whole body, bone marrow and other organs, and 21 rem thyroid.

The procedures for estimating genetic risks are less precise than those for somatic risks, and it is therefore necessary to give a range for the genetic dose that is considered equivalent to the risk of two standard errors of the mean for natural radiation. The range of genetic dose values is 0.07 to 1.73 rem for the preventive PAG and 1 to 24 rem for the Emergency PAG.

Risks can be compared to the risks from natural disasters for the purpose of determining their acceptability. The radiation doses equivalent to the risk for natural disaster (taken as one in a million annual individual risk of death) are 1.01 rem to the whole body or bone marrow for the preventive PAG and 15 rem for the emergency PAG. These values are quite consistent with the dose of 0.47 rem for the Preventive PAG and 7 rem for the Emergency PAG that are equivalent to the risk of two standard errors of the mean natural radiation dose.

To obtain some perspective of the economic impact of the PAG's as a function of the numerical level recommended, NRC performed a cost-effectiveness analysis using existing data. The cost-effectiveness analysis was done for two models based on projected incidents with different magnitudes of the radioactive release from light-water nuclear power plants. Under the limited scenarios investigated, the rate of change in costs for condemnation of milk drops rapidly when interdiction criteria are between a 0.5 and 10 rem dose commitment to the infant thyroid. The rate of change drops more gradually when the criteria are between 10 and 20 rem, and the rate of change only moderately drops following an interdiction criterion of greater than 20 rem.

the Commissioner concludes that it is prudent to recommend in proposed § 1090.400(c) numerical limits for the Preventive PAG equivalent to 0.5 rem dose commitment to the whole body, bone marrow, or other organs, and 1.5 rem dose commitment to the thyroid gland. Numerical limits for the Emergency PAG are recommended at 5 rem and 15 rem, respectively, representing a factor of 10 over the Preventive PAG.

In summary, the Preventive and Emergency PAG's refer to projected dose commitments to an individual in the exposed population. For the Preventive PAG the most critical segment of the population consists of newborn infants or children less than 1 year of age. For the Emergency PAG two critical segments are defined: (1) An infant group and (2) an adult group (excluding young children). This definition permits a greater flexibility in cases where exposure can be limited to adults only because children are more easily removed from the area of contamination or their diet limited to canned or other stored food.

Applicability

Proposed § 1090.400(a) applies the recommended PAG's to many types of contaminating events, including accidents at nuclear facilities, tansportation accidents, and fallout from nuclear devices under peacetime conditions. Several radionuclides are considered particularly important and receive special attention in calculation of derived response levels. These are iodine-131, cesium-137, strontium-90, and strontium-89, which are relatively abundant among the fission products, enter the food chain easily, and are taken up and retained by the human body.

For transportation accidents the greatest hazard may be from the potential consequences of long-lived gamma emitters such as cobalt-60 and alhpa emitters such as plutonium. For man, due to limited absorption through the gastrointestinal tract, these radionuclides are unlikely to have as great an impact through the

human food chain as the radionuclides mentioned above; however, the proposed regulation refers to sources in the literature from which dose commitments to the gastrointestinal tract can be determined, should the need arise.

For other radionuclides not specified in the recommendations, the proposed response levels for the Preventive and Emergency PAG's may be calculated for individual radionuclides deposited on soil or pasture or present in milk or other foods based on dose commitment factors available in the literature (Refs. 2, 11, and 12).

Specific response levels are proposed for initial deposition, concentration in grazed forage and milk, and total radionuclide intake. The proposed recommendations suggest a method for relating individual food constituents to the total diet. Thus, response levels can be calculated for an appropriate PAG for individual foods that could be significant because of their relative proportion in the total diet by weight and/or high radionuclide concentrations.

Initial deposition on animal feeds, other than pasture, should be dealt with on a case-by-case basis, taking into consideration retention of the radionuclide in the particular feed and the relationship between radionuclide concentration in the animal feed and the concentration of radionuclides in human food. For hay or silage fed to lactating cows, the initial deposition should not exceed that equivalent to the recommendations for grazed forage (pasture).

Sampling

It is important that sampling be carried out at a site which permits sufficient time for action to be taken at an appropriate stage in the farm-processor-market cycle, and that the method of radionuclide measurement be predicated upon the specific response level. Proposed § 1090.400(f) recommends the retail market, processing plant, and farm as sampling sites. Proposed methods of measuring radionuclides in food and animal feeds recommended in § 1090.400(g) would meet the following criteria: (1) The complexity of the method decreases as the need for more rapid action increases; and (2) the sensitivity and selectivity of the method decreases with an increase in the level of detectability required. Methodology referred to in these recommendations includes precise, albeit complex, laboratory methods, rapid methods employing simple laboratory or modified field techniques, and field methods using a simple Geiger-Mueller detector. No action should be initiated without prior verification of the analysis.

Protective Action

Protective action can be initiated at the source or at the beginning of the food chain (soil, vegetation, or cattle), applied to the intermediate vector prior to ingestion by man (milk or food), or administered to the population itself. For the purpose of these proposed recommendations the Commissioner expects specific actions would be limited to the food chain.

The most efficient protective action should be taken. Therefore, an attempt should be made to achieve a reasonable cost-benefit ratio.

The Commissioner emphasizes that prior to taking protective action, the responsible officials should weigh the health benefits to be gained from a reduction in radiation dose against the costs of disrupting the food supply. In this respect, the population to benefit from the dose reduction may not be the same as that receiving the impact. It is probable that both the State in which the contaminating event occurs and adjacent States may be involved; coordination among these affected jurisdictions would be essential and would require a knowledgeable consideration of all pertinent factors. Because this may involve a broad range of informed participation, the Commissioner recommends that if an action with a major impact is contemplated, the food processing and food distribution agencies and industries, as well as the health and agricultural agencies, be consulted. These recommendations envision that the contamination of food in the event of a radiation incident will be controlled at the State and local levels. However, should food in interstate commerce become involved, FDA will use these PAG recommendations as the basis for regulatory action.

References

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5. Environmental Protection Agency, "Manual of Protective Action Guides and Protective Actions for Nuclear Incidents," EPA 520/1-75-001, September 1975.

6. Federal Radiation Council, Memorandum for the President, "Raidation Protection Guidance for Federal Agencies," *Federal Register,* May 18, 1960.

7. Federal Radiation Council, Memorandum for the President, "Radiation Protection Guidance for Federal Agencies," *Federal Register,* Sept, 26, 1961, as corrected.

8. Federal Radiation Council, Memorandum for the President, "Radiation Protection Guidance for Federal Agencies," *Federal Register,* July 16 and Aug. 22, 1964.

9. Federal Radiation Council, Memorandum for the President, "Radiation Protection Guidance for Federal Agencies," *Federal Register,* May 22, 1965.

10. National Academy of Sciences, National Research Council, "The Effects on Populations of Exposure to Low Levels of Ionizing Radiation," Report of the Advisory Committee on the Biological Effects of Ionizing Radiation (BEIR), 1972.

11. Ng, Y. C., C. A. Burton, S. E. Thompson, R. K. Tandy, H. K. Kretner, and M. W. Pratt, "Prediction of the Maximum Dosage to Man from the Fallout of Nuclear Devices, IV. Handbook for Estimating the Maximum Internal Dose from Radionuclides Released to the Biosphere, Lawrence Radiation Laboratory," UCRL-50163 Part IV, 1968.

12. U.S. Nuclear Regulatory Commission, Regulatory Guide 1.109, "Calculation of Annual Doses to Man from Routine Releases of Reactor Effluents for the Purpose of Evaluating Compliance with 10 CFR Part 50," Appendix I, Oct. 1977.

13. Lowrance, W. W., "Of Acceptable Risk," William Kaufmann Inc., Los Altos, CA, p. 8-11, 1976.

Pertinent background data and information on the guidelines proposed herein are on file in the office of the Hearing Clerk (HFA-305), Food and Drug Administration, and copies are available from the address above.

The Commissioner has carefully considered the environmental effects of the proposed regulation and, because the proposed action will not significantly affect the quality of the human environment, has concluded that an environmental impact statement is not required. A copy of the environmental impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

Therefore, under the Public Health Service Act (secs. 301, 310, 311, 58 Stat. 691-693 as amended, 88 Stat. 371 (42 U.S.C. 241, 242o, 243)) and authority delegated to him (21 CFR 5.1), the Commissioner proposes to amend Part 1090 by establishing Subpart E consisting of § 1090.400, to read as follows:

Subpart E—Emergency Radiation Protection Recommendations

§ 1090.400 Recommendations on protective action planning for human food and animal feeds.

(a) *Applicability.* These guidelines are recommended for use by appropriate State or local agencies in response planning and the conduct of radiation protection activities involving the production, processing, distribution, and use of human food and animal feed in the event of an accident resulting in

the release of radioactivity to the environment. The Food and Drug Administration recommends that this guidance be used on a case-by-case basis to determine the need for taking appropriate protective action. These recommendations are intended for implementation within hours or days from the time an emergency is recognized, and their duration should not exceed 1 or 2 months. Protective actions are appropriate when the health benefits associated with the reduction in exposure to be achieved are sufficient to offset the undesirable features of the protective actions. The Protective Action Guides in paragraph (c) of this section represent judgments as to when corresponding protective actions are justified.

(b) *Definitions.* (1) "Dose" is a general term denoting the quantity of radiation or energy absorbed. For special purposes it must be appropriately qualified. In these recommendations it refers specifically to the term "dose equivalent."

(2) "Dose commitment" means the radiation dose equivalent received by an exposed individual to the organ cited over a lifetime from a single event.

(3) "Dose equivalent" is a quantity that expresses all radiation on a common scale for calculating the effective absorbed dose. It is defined as the product of the absorbed dose in rads and certain modifying factors. The unit of dose equivalent is the rem.

(4) "Projected dose commitment" means the dose commitment that would be received in the future by individuals in the population group from the contaminating event if no protective action were taken.

(5) "Protective action" means an action taken to avoid most of the exposure to radiation that would occur from future ingestion of foods contaminated with radioactive materials.

(6) "Protective action guide" (PAG) means the projected dose commitment values to individuals in the general population that warrant protective action following a release of radioactive material. Protective action would be warranted if the expected individual dose reduction is not offset by negative social, economic, or health effects. The PAG does not include the dose that has unavoidably occurred prior to the assessment.

(7) "Rad" means the unit of absorbed dose equal to 0.01 Joule per kilogram in any medium.

(8) "Rem" is a special unit of dose equivalent. The dose equivalent in rems is numerically equal to the absorbed dose in rads multiplied by the quality factor, the distribution factor, and any other necessary modifying factors.

(9) "Response level" means the activity of a specific radionuclide (1) initially deposited on pasture; or (2) per unit weight or volume of food or animal feed; or (3) in the total dietary intake which corresponds to a particular PAG.

(c) *Protective action guides (PAG).* To permit flexibility of action for the reduction of radiation exposure to the public via the food pathway due to the occurance of a contaminating event, the following Preventive and Emergency Protective Action Guides for an exposed individual in the population are adopted:

(1) *Preventive PAG* which is (i) 1.5 rem projected dose commitment to the thyroid, or (ii) 0.5 rem projected dose commitment to the whole body, bone marrow, or any other organ.

(2) *Emergency PAG* which is (i) 15 rem projected dose commitment to the tryroid, or (ii) 5 rem projected dose commitment to the whole body, bone marrow, or any other organ.

(d) *Response levels equivalent to PAG.* Although the basic PAG recommendations are given in terms of projected dose equivalent, it is often more convenient to utilize specific radionuclide concentrations upon which to initiate protective actions. Derived response levels equivalent to the PAG's for radionuclides of interest are:

(1) *Response level for Preventive PAG.*

Infant [1] *as critical segment of population*

	131_I [2]	137_{Cs}	90_{Sr}	89_{Sr}
Initial deposition (microcuries/meter) [2]	0.14	1.7	0.34	6
Peak activity:				
Pasture (microcuries/kilogram) [3]	0.27	3.5	0.7	13
Milk (microcuries/liter)	0.012	0.34	0.007	0.13
Total intake (microcuries)	0.09	7	0.2	2.6

[1] Newborn infant critical segment of population for iodine-131. For other radionuclides, "infant" refers to child less than 1 year of age.

[2] From fallout, iodine-131 is the only radioiodine of significance with respect to milk contamination beyond the first day. In case of a reactor accident the cumulative intake of iodine-133 via milk is about 0.5 percent of iodine-131 assuming equivalent deposition.

[3] Fresh weight.

(2) *Response level for Emergency PAG.* The response levels equivalent to the Emergency PAG are presented for both infants and adults, to permit use of either level and thus assure a flexible approach to taking action in cases where exposure of the most critical portion of the population (infants and pregnant women) can be prevented:

	131_I [3]		137_{Cs}		90_{Sr}		89_{Sr}	
	Infant [1]	*Adult*	*Infant* [2]	*Adult* [5]	*Infant* [2]	*Adult*	*Infant* [2]	*Adult*
Initial deposition (microcuries/meter [2])	1.4	18	17	65	3.4	25	60	3,000
Peak activity:								
Pasture (microcuries/kilogram) [4]	2.7	37	35	50	7	50	130	6,000
Milk (microcuries/liter)	0.12	1.7	3.4	22	0.08	0.55	1.3	60
Total intake (microcuries)	0.9	10	70	110	2	12	26	1,000

[1] Newborn infant critical segment of population for iodine-131.

[2] "Infant" refers to child less than 1 year of age.

[3] From fallout, iodine-131 is the only radioiodine of significance with respect to milk contamination beyond the first day. In case of a reactor accident the cumulative intake of iodine-133 via milk is about 0.5 percent of iodine-131 assuming equivalent deposition.

[4] Fresh weight.

[5] Response levels for the adult population for cesium-137 refer to the meat pathways.

[6] Peak activity in meat, microcurie per kilogram.

(e) *Implementation.* When using the PAG's and associated response levels for response planning or protective actions, the following conditions should be followed:

(1) *Specific food items.* To obtain the response level (microcurie/kilogram or liter) equivalent to the PAG for other specific foods, it is necessary to weigh

the contribution of the individual food to the total dietary intake; thus,

Response level for a single food item (microcurie/kilogram or liter)=Response level (total intake) ÷ dietary factor × intake factor × days of intake

(i) The "intake factor" is 1 kilogram per day for the infant and 2.2 kilograms per day for the adult. Tap water is included in the adult intake and represents about 10 percent of the total intake. Dietary factors based on average consumption that may be used for other foods are as follows:

Group	Food Items	"Dietary factor" for any single food item in the group
I	Liquid Milk	0.70 for infants and children less than 1 year of age. 0.25 adults.[1]
II	Meat, bakery products, fresh vegtables, fresh fruit, beverages (excluding those individually listed)	0.10.
III	Fats and oils, potatoes and seeet potatoes, flour and cereal, poultry, eggs, sugar and sweeteners, canned, frozen, and dried vegetables	0.05.
IV	Condiments, spices and flavoring agents, fish and shellfish, canned frozen and dried fruit, vegetable and fruit juices, soups and gravies, nuts and peanut butter	0.02.

[1]This value is based on the calcium equivalent, i.e., the quantity of whole fluid milk to which dairy products are equivalent in calcium content. It includes cream, cheese, and ice cream.

(ii) For population groups having significantly different dietary intakes, an appropriate adjustment of dietary factors should be made.

(2) *Radionuclide mixtures.* If a mixture of radionuclides is present, the sum of all the ratios of the concentration of each specific radionuclide to its specific response level equivalent to the PAG should be less than one.

(3) *Other radionuclides.* The response level for the Preventive and Emergency PAG for other radionuclides should be calculated from dose commitment factors available in the literature (Ng, Y. C. et al. (1968), UCRL-50163; Cowser, K. E. et al., ORNL-4101 (1967); and U.S. Nuclear Regulatory Commission Reg. Guide 1.109 (1977)).

(4) *Other critical organs.* Dose commitment factors in the literature cited in paragraph (e)(3) of this section refer to bone rather than bone marrow dose commitments. For the purpose of these recommendations dose commitment to the bone marrow is considered to be 0.3 of the bone dose commitment. This is based on the ratio of dose rate per unit activity in the bone marrow to dose rate per unit activity in a small tissue-filled cavity in bone and assumes that the strontium-90 is distributed only in the mineral bone (Spiers, F. W. et al., in "Biomedical Implications of Radiostrontium Exposure," AEC Symposium 25, (1972)). The ratio for strontium-89 is the same because the mean particle energies are similar (0.56 MeV(megaelectronvolts)). Situations could arise in which an organ other than those discussed in this paragraph could be considered to be the organ receiving the highest dose per unit intake. In the case of exposure via the food chain, depending on the radionuclide under consideration, the gastrointestinal tract could be the primary organ exposed. The references cited in paragraph (e)(3) of this section contain dose commitment factors for the following organs: bone, kidneys, liver, ovaries, spleen, whole body, and gastroinstestional tract.

(5) *Animal feeds other than pasture.* Animal feeds, other than pasture, should be dealt with on a case-by-case basis taking into consideration the relationship between the radionuclide concentration in the animal feed and the concentration of the radionuclide in human food. For hay and silage fed to lactating cows, the concentration should not exceed that equivalent to the recommendations for pasture.

(f) *Sampling paramenter* Generally, sites for sample collection should be the retail market, the processing plant, and the farm.

(g) *Recommended methods of analysis.* Techniques for measurement of radionuclide concentrations should have detection limits equal to or less than the response levels equivalent to a specific PAG. Some useful methods of radionuclide analysis can be found in: (1) Laboratory Methods-"HASL Procedure Manual," edited by John H. Harley, HASL 300, ERDA, Health and Safety Laboratory, New York, NY, 1973; "Rapid Methods for Estimating Fission Product Concentrations in Milk," U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 999-R-2, May 1963; "Evaluation of Ion Exchange Cartridges for Field Sampling of Iodine-131 in Milk," Johnson, R. H., and T. C. Reavy, *Nature,* 208, (5012):750-752, Nov. 20, 1965; and (2) Field Methods—Kearny, C. H., ORNL 4900, Nov. 1973; Distenfeld, C., and J. Klemish, Brookhaven National Laboratory, to be published; and International Atomic Energy Agency, "Environmental Monitoring in Emergency Situations," 1966. Analysis need not be limited to these methodologies but should provide comparable results. No action should be taken without verification of the analysis.

(h) *Protective actions.* Actions are appropriate when the health benefit associated with the reduction in dose that can be achieved is considered to offset the undesirable health, economic, and social factors. It is the intent of these recommendations that not only the protective actions cited for the Emergency PAG be initiaited when the equivalent response levels are reached, but also that actions appropriate at the Preventive PAG be considered. This has the effect of reducing the period of time required during which the protective action with the greater economic and social impact needs to be operative. Once one or more protective actions are initiated, it is recommended that the action or actions continue for a sufficient time to avoid most of the projected dose. There is a longstanding FDA policy on the purposeful blending of adulterated and unadulterated food. The following protective actions should be considered for implementation when the projected dose equals or exceeds the appropriate PAG:

(1) *Preventive PAG*—(i) For pasture: (*a*) Removal of lactating dairy cows from contaminated pasturage and substitution of uncontaminated stored feed.

(*b*) Substitute source of uncontaminated water.

(ii) For milk: (*a*) Withholding of contaminated milk from the market to allow radioactive decay of short-lived radionuclides. This may be achieved by storage of frozen fresh milk, frozen concentrated milk, or frozen concentrated milk products.

(*b*) Storage for prolonged times at reduced temperatures also is feasible provided ultrahigh temperature pasteurization techniques are employed for processing (Finley, R. D., H. B. Warren, and R. E. Hargrove, "Storage Stability of Commercial Milk," *Journal of Milk and Food Technology,* 31(12):382-387, December 1968).

(*c*) Diversion of fluid milk for production of dry whole milk, nonfat dry milk, butter, or evaporated milk.

(iii) For fruits and vegetables: (*a*) Washing, brushing, scrubbing, or peeling to remove surface contamination.

(*b*) Preservation by canning, freezing, and dehydration or storage to permit radioactive decay of short-lived radionuclides.

(iv) For grains: (*a*) Milling and (*b*) polishing.

(v) For other food products, processing to remove surface contamination.

(vi) For meat and meat products, consider on a case-by-case basis.

(vii) For animal feeds: (*a*) Actions relative to animal feeds, other than pasture, should be carried out on a case-by-case basis.

(*b*) Increase noncontaminated mineral calcium to a maximum.

(2) *Emergency PAG.* Responsible officials should isolate food containing radioactivity to prevent its introduction into commerce and determine whether condemnation or another disposition is appropriate. Before taking this action, the following factors should be considered:

(i) The availability of other possible protective actions discussed in paragraph (h)(1) of this section.

(ii) Relative proportion of the total diet by weight represented by the item in question.

(iii) The importance of the particular food in nutrition and the availability of uncontaminated food or substitutes having the same nutritional properties.

(iv) The relative contribution of other foods and other radionuclides to the total projected dose.

(v) The time and effort required to effect corrective action.

Interested persons may, on or before February 13, 1979, submit to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, written comments regarding this proposal. Four copies of all comments shall be submitted, except that individuals may submit single copies of comments, and shall be identified with the Hearing Clerk docket number found in brackets in the heading of this document. Received comments may be seen in the above office between the hours of 9 a.m. and 4 p.m., Monday through Friday.

NOTE.—The Food and Drug Administration has determined that this proposal will not have a major economic impact as defined by Executive Order 11821 (amended by Executive Order 11949) and OMB Circular A-107. A copy of the economic impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

Dated: December 8, 1978.

DONALD KENNEDY,
Commissioner of Food and Drugs.

[FR Doc. 78-34860 Filed 12-14-78; 8:45 am]

[4110-03-M]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[Docket No. 78D-0343]

POTASSIUM IODIDE AS A THYROID-BLOCKING AGENT IN A RADIATION EMERGENCY

Request for Submissions of New Drug Applications and Notice of Availability of Labeling Guidelines

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) requests submissions of new drug applications (NDA's) for potassium iodide in oral dosage forms for use as a thyroid-blocking agent in a radiation emergency. The approval of oral dosage forms of potassium iodide as a thyroid-blocking agent for use in a radiation emergency would be one step in meeting the responsibilities of the Department of Health, Education, and Welfare (DHEW) to State and local governments for radiological emergency response planning. The agency encourages interested persons to submit NDA's in the interest of the public safety. The agency is also announcing the availability of labeling guidelines for potassium iodide for such use.

ADDRESS: Submit new drug applications to the Food and Drug Administration, Division of Metabolism and Endocrine Drug Products (HFD-130), Rm. 14B04, 5600 Fishers Lane, Rockville, MD 20857. Comments concerning the labeling guideline and requests for copies of the guideline should be sent to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Edwin V. Dutra, Jr., Bureau of Drugs (HFD-30), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-6490.

SUPPLEMENTARY INFORMATION: By FEDERAL REGISTER notice of December 24, 1975 (40 FR 59494), the General Services Administration (GSA) outlined the responsibilities of several Federal agencies concerning certain emergency response planning guidance that the agencies should provide to State and local authorities. The Department of Health, Education, and Welfare (DHEW) is responsible for assisting State and local authorities in developing plans for preventing adverse effects from exposure to radiation in the event that radioactivity is released into the environment. These plans are to include the prophylactic use of drugs that would reduce the radiation dose to specific organs due to the sudden release into the environment of large quantities of radioactivity that might include several radioactive isotopes of iodine.

BACKGROUND

The GSA notice of December 24, 1975, concluded that there is an exceedingly low probability that incidents will occur involving either the use of radioactive materials in fixed nuclear facilities or the transportation of those materials. Because of the possible increase in number of nuclear power plants, however, several Federal agencies are identifying those possibilities, however remote, that could adversely affect the public, should an incident occur. One possibility is the sudden release of large quantities of radionuclides, which might include a number of isotopes of radioiodine, into the environment. When radioiodines are inhaled or ingested, they rapidly accumulate in the thyroid gland and are metabolized into organic iodine compounds. These compounds could reside in the thyroid gland long enough to allow for local radiation damage, resulting in thyroiditis, hypothyroidism, or thyroid neoplasia with either benign or malignant characteristics. Therefore, it is considered in the public interest that State and local authorities be prepared to take effective measures to prevent or curtail markedly the accumulation of radioiodines by the thyroid gland, should such an incident occur. These measures may include the use of a thyroid-blocking agent.

An ad hoc committee to the National Council on Radiation Protection and Measurements (NCRP), which included FDA representatives as consultants, studied the feasibility of using certain drug products as thyroid-blocking agents to reduce radiation dose to the thyroid gland. The NCRP, located in Bethesda, Maryland, is a nonprofit corporation chartered by Congress in 1964 to collect, analyze, develop, and disseminate information and recommendations about radiation protection. The NCRP is made up of 56 scientific committees, composed of experts having detailed knowledge and competence in the particular area of the committee's interest. An NCRP report published August 1, 1977 (NCRP Report No. 55, "Protection of the Thyroid Gland in the Event of Release of Radioiodine") discusses the safety and efficacy of thyroid-blocking agents and recommends that potassium iodide be considered for thyroid-blocking purposes under certain emergency conditions.

The report discusses stockpiling thyroid-blocking agents at appropriate outlets for ease of distribution in the event their use is necessary in a radiation emergency. The report concludes, however, that the details of stockpiling, if this method is to be used, and of distribution would be determined best at the State and local levels.

ANALYSIS

The Commissioner of Food and Drugs has analyzed the NCRP report and the available scientific literature about the possible prophylactic use of drugs to reduce the radiation dose to the thyroid gland in a radiation emergency. Although a variety of chemical substances can block the accumulation of radioiodine in the thyroid gland, iodide in the form of potassium iodide appears to be most suitable for this purpose. A number of factors were considered in choosing iodide (and specifically potassium iodide) over other blocking agents such as propylthiouracil, methimazole, perchlorate, thiocyanate, or iodate. These factors included the degree of the blocking achieved, the rapidity on onset of the blocking effect, the duration of the blocking effect, and the safety of the blocking agent. Although iodide acts on the thyroid gland in several ways, its use in this instance is primarily predicated on its ability to saturate the iodide transport system, and thus effectively abolish entry of radioiodine except for small amounts that might enter the gland by diffusion. Almost complete (greater than 90 percent) blocking of peak radioactive iodine uptake by the thyroid gland can be obtained by the oral administration of 100 milligrams (mg) of iodide (130 mg of potassium iodide) just before or at the time of exposure. A smaller dose (65 mg of potassium iodide) can be used in infants under 1 year of age. A daily dose is required to maintain the blocked state. The use of a blocking agent is not expected to exceed about 10 days.

Experiments designed to study the rapidity of onset of blocking have shown that at a 100-mg dose of iodide, the onset of blocking is readily demonstrated 30 minutes after oral administration. The decay of the blocking effect after cessation of iodide administration is relatively slow, so that a daily dose of 100 mg of iodide (130 mg of potassium iodide) appears to maintain effective blocking. To have the greatest effect in decreasing the accumulation of radioiodine in the thyroid gland, the thyroid-blocking agent should be administered immediately before or after initial exposure. A substantial benefit (e.g., a block of 50 per-

cent) is attainable, however, when the blocking agent is first given within 3 to 4 hours after acute exposure. If a person is exposed to radioiodine when circumstances do not permit the immediate administration of potassium iodide, the initial administration will be of some limited benefit even as long as 12 hours after exposure.

Although most of the radioiodine that is not taken up by the thyroid gland is excreted in the urine within 48 hours, the radioiodine that is taken up by, and accumulated in, the thyroid gland may be "leaked" back into the general circulation system as a consequence of intrathyroidal metabolism. Thus, there is a possibility that circulating and recirculating radioiodine may be taken up by the thyroid gland (from the circulatory system) even though there are no radioiodines remaining in the environment. To prevent or curtail the accumulation of radioiodine by the thyroid gland from any source, including chronic exposure, a daily dose of a thyroid-blocking agent is necessary for a period of time after exposure. The duration of time that a blocking agent would be required is not expected to exceed about 10 days. A minimum of 3 to 7 days of daily administration is anticipated based on the biological events described above and the effective half-life of ^{131}I.

Potassium iodide has been used widely for many years in the treatment of bronchial asthma and other pulmonary disorders. Daily oral doses of potassium iodide ranging from 300 to 1200 mg have been given to asthmatics over long periods of time. Daily oral doses of potassium iodide of 100 mg or greater have been administered in cough preparations to children. Although a variety of adverse reactions have been reported in connection with the use of potassium iodide, these reactions are considered, in general, to be directly proportional to the dose and duration of therapy, and most toxicity has been related to chronic administration (see pp. 38357-38358 of the findings of the Advisory Review Panel on Over-the-Counter (OTC) Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Drug Products, published in the FEDERAL REGISTER of September 9, 1976 (41 FR 38312)). In addition to its use in pulmonary disorders, potassium iodide is used in daily doses ranging from 250 to 300 mg in patients for up to 3 weeks in connection with the diagnostic use of radiopharmaceutical drug products to block the uptake of radioiodine by the thyroid gland. The Commissioner is unaware of reports of significant toxicity with this use of potassium iodide.

CONCLUSIONS

The Commissioner concludes that potassium iodide is safe and effective for use as a thyroid-blocking agent in a radiation emergency under certain specified conditions of use because it has been widely used for many years, in large doses, and on a long-term basis with an incidence of side effects and toxicities, in general, proportional directly to dose and duration of therapy. The risks from the short-term use of relatively low doses of potassium iodide in a radiation emergency are outweighed by the risks involved from exposure to radioiodine. However, the Commissioner does not believe that potassium iodide has been used to such an extent or for a period of time under these specified conditions to permit the conclusion that the drug is generally recognized as safe and effective. Accordingly, it is regarded as a new drug requiring an approved new drug application as a condition of marketing. Thus, the Commissioner will accept new drug applications meeting the requirements of § 314.1 (21 CFR 314.1). Because of the publicly available safety and efficacy data documenting the drug's use, the safety and efficacy requirements of § 314.1 may be met by citing the published literature in the List of Material Consulted (below) documenting its use. The Commissioner advises that it is unnecessary to submit (1) copies and reprints of the data cited in the List of Material Consulted in this document, and (2) copies and reprints contained in the journals listed in § 310.9 (21 CFR 310.9). Both the safety and efficacy data upon which the Commissioner bases the above conclusions and NCRP Report No. 55, "Protection of the Thyroid Gland in the Event of Release of Radioiodine," are on file for public inspection in the office of the Hearing Clerk, Food and Drug Administration. The Commissioner invites applicants to submit any other pertinent studies and literature of which they are aware.

The Commissioner also believes for this specific use of potassium iodide, and at the dosages intended, that the prescription-dispensing requirements of section 503(b)(1) (21 U.S.C. 353(b)(1)) of the Federal Food, Drug, and Cosmetic Act are unnecessary. Only the chronic administration of daily doses of potassium iodide far in excess of those necessary for thyroid-blocking in a radiation emergency have resulted in significant side effects and toxicities. These problems should not occur from the short-term use of a relatively low daily dose of potassium iodide. However, the Commissioner advises that the conclusion that a potassium iodide drug product manufactured for use as a thyroid-blocking agent in a radiation emergency is suitable for OTC sale does not affect the present status as a prescription drug of a potassium iodide drug product manufactured for other uses or at higher dosages.

The importance to the public of ready and convenient access to this product and the unlikelihood that it will be needed reinforce the Commissioner's belief that potassium iodide as a thyroid-blocking agent in a radiation emergency should be considered suitable for OTC use. The Commissioner also believes that special labeling directed to the patient must accompany the immediate container of these OTC preparations to ensure they are used safely and effectively. A labeling guideline that describes the kind of information to be included on the container label, if space permits, and if the accompanying labeling is on file with the Hearing Clerk, FDA. The guideline sets forth specific language that would be acceptable to the agency.

The guideline is entitled "Guideline Labeling for Potassium Iodide for Use as a Thyroid-Blocking Agent in a Radiation Emergency."

The person responsible for maintaining the guideline labeling is JoAnne C. Marrone, Food and Drug Administration, Division of Metabolism and Endocrine Drug Products (HFD-130), Room 14B04, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3520. Copies of the guideline are available from the Hearing Clerk (address above).

LIST OF MATERIAL CONSULTED

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8. Cole, R., "Inhalation of Radioiodine from Fallout: Hazards and Counter Measures," Contract No. DAHC20-70-C-0381, Defense Civil Preparedness Agency, Office of

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9. Saxena, K. M. et al., "Minimal Dosage of Iodide Required to Suppress Uptake of Iodine-131 by Normal Thyroid," *Science*, 138:430-431, 1962.

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12. National Council on Radiation Protection Report No. 55, "Protection of the Thyroid Gland in the Event of Releases of Radioiodine," National Council on Radiation Protection and Measurements, August 1, 1977.

13. General Services Administration FEDERAL REGISTER notice, 40 FR 59494, December 24, 1975.

14. Talbot, J. M., K. D. Fisher, and C. J. Carr, "A Review of the Significance of Untoward Reactions to Iodine in Foods," Report of the Federation of American Societies for Experimental Biology under FDA Contract Number 71-294, September 1974.

15. Maxon, H. R. et al., "Ionizing Irradiation and the Induction of Clinically Significant Disease in the Human Thyroid Gland," *American Journal of Medicine*, 63:967-978, 1977.

16. Radiation-Associated Thyroid Carcinoma, Edited by L. J. DeGroot with L. A. Frohman, E. L. Kaplan, and S. Refetoff; Grune and Stratton, Inc. publishers, 1977.

17. Lengemann, F. W. and J. C. Thompson, Jr., "Prophylactic and Therapeutic Measures for Radioiodine Contamination," *Health Physics*, 9:1391-1397, 1963.

18. Pochin, E. E. and C. F. Barnaby, "The Effect of Pharmacological Doses of Non-Radioactive Iodide on the Course of Radioiodine Uptake by the Thyroid," *Health Physics*, 7:125-126, 1962.

19. Conard, R. A. et al., "A Twenty Year Review of Medical Findings in a Marshallese Population Accidentally Exposed to Radioactive Fallout," Report BNL-50424, Brookhaven National Laboratory, Upton, NY, 1975.

20. Goodman, L. S. and A. Gilman, *The Pharmacological Basis of Thereapeutics*, 5th Ed., MacMillan Publishing Co., Inc., New York, pp. 801, 802, 1975.

The agency encouraged interested persons to submit written comments (preferably four copies, specifying Hearing Clerk docket no. 78D-0343) on the guideline labeling to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857. If, as a result of comments received on the guideline labeling, the Commissioner determines that the labeling should be revised, a notice will be published in the FEDERAL REGISTER announcing that such changes have been made.

The Commissioner has determined that this document does not contain an agency action covered by § 25.1(b) (21 CFR 25.1(b)) and, therefore, consideration by the agency of the need for preparing an environmental impact statement is not required.

Dated: December 8, 1978.

DONALD KENNEDY,
Commissioner of Food and Drugs.

[FR Doc. 78-34843 Filed 12-14-78; 8:45 am]

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